UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,308	10/24/2003	Frank Grosveld	CARP0015-100	1498

34132 7590 02/12/2007

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,308	GROSVELD, FRANK	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,10,11 and 17-38* is/are pending in the application.

4a) Of the above claim(s) *17-32 , 37-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,10,11 and 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' supplementary amendment to the claims and specification filed November 14, 2006 has been received and entered. It is noted that applicants had also filed an amendment on October 19, 2006, which did not correctly use claim identifiers. Applicants have amended claims 1-4, 7-8, 10-11, while claim 5-6, 9 and12-16 have been canceled. Applicants have also added claim 33-38.

Claims 1-4, 7-8, 10-11, 17-38 are pending in this application.

Election/Restrictions

Applicant's election with traverse of group I in the response filed dated April 27, 2006 was acknowledged. The traversal was on the ground(s) that Group I and Group II-III should be examined together because search for invention of Group I would be coextensive with Group II and III. In addition, applicants asserted that only method of Group I would be required to make the antibody recited in Groups II and III. Applicant's arguments for examining elected method group with the product claims were not persuasive because as recited VHH single chain antibody can be made by another process. Riechmann et al (J Immunol Methods. 1999; 231(1-2): 25-38) taught an intact heavy chain antibody that was readily generated by cloning a particular camel VH in front of the hinge and effector function domains of human IgG1 as stated in previous office action. Applicants argue that as amended claims embrace single chain antibodies that are produced in response to antigen challenge in B cell that is different from the method disclosed by Riechmann. It is emphasized that method disclosed by Riechmann et al also produces VHH antibody by using another method. In addition, applicants have received office action on originally presented claims; any subsequent amendment in response to office action would not change the restriction requirement on originally presented claims directed to distinct methods and composition as stated in the restriction requirement sent on 2/27/2006.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-32 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. It is noted that claims 33-36 are generally drawn to elected method steps, while newly added claims 37-38 further comprises additional steps for the production of monoclonal antibody which is not directed to the elected claims, Therefore claims 37-38 are also withdrawn as being brawn to a nonelected invention.

Claims 1-4, 7-8, 10-11 and 33-36 are under consideration.

Drawings

The drawing submitted on 10/19/2006 is objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: "Replacement Sheet". Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Withdrawn-Specification

The objection to the specification is withdrawn in view of amendment to the specification filed 11/14/2006.

Withdrawn-Double Patenting

Claims 1-16 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-16 of copending Application No. 10/693308 is withdrawn in view of amendments in pending claims by changing the breadth of the claims in the instant application.

New-Claim Rejections – Necessitated by amendments- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-8, 10-11 remain rejected under 35 U.S.C. 112 and 33-36 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the instant case, claims are directed to a method for the production of a VHH or camelised VH single heavy chain heavy chain antibody in a mammal comprising the step of expressing a heterologous VHH heavy chain locus in that mammal.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by

Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

The aspects considered broad are: breadth of subject population for expressing VHH heavy chain locus, any vector comprising any promoter or locus control region for expressing VHH specifically in B cells, using ES cells of any species and expressing VHH locus.

The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any nonhuman mammal. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of expressing VHH heavy chain loci in any nonhuman mammal *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced. As will be shown below, broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

As a first issue, the claims 1-4, 7-8, 10-11 and 33-36 embrace for the production of a single heavy chain antibody in a nonhuman mammal comprising the step of expressing a heterologous VHH heavy chain locus in that mammal specifically in B cell in response to an antigen challenge. The specification contemplates using vector such as YAC or BAC that is suitable of inserting large amounts of nucleic acid, sufficient to

encode an entire immunoglobulin heavy chain locus (pp 15, lines 14-23). The specification further contemplates making transgenic mice that is capable of producing fully functional specific single chain VHH antibody which undergoes a process of evolution similar or the same as that of camelid antibodies produced in their native environment. However, the specification provides only prophetic and a general methodology without disclosing any specifics. The specification only provides prophetic reference to most of the method steps without giving any sequence information for the YAC or BACs. The specification also fails to provide any sequence information for the vectors that would be required for multi step cloning process for expressing transgene *in vivo*. The disclosed figure 1 does not provide sufficient details to enable one skilled in the art to recreate the complex cloning process prophetically taught in the specification for generating VHH single chain antibody locus using any vector, particularly as the sequence and structure of such a BAC or YACs is not known. As amended instant claims require VHH heavy chain locus to be expressed specifically in B cells in response to antigen challenge. It is apparent that each method of expressing single chain VHH locus in different subject requires further experimentation that is not routine and subject to variation in anticipated class switching as contemplated by specification.

As a second issue, the scope of invention as claimed encompasses a method for producing VHH single chain antibody in any nonhuman mammal. It has been difficult to predict the method as contemplated in the specification would result in functional VHH antibody. For example, De Genst et al (Dev Comp Immunol. 2006; 30(1-2): 187-98) in a post filing art while reviewing the state of antibody repertoire development in camelids state "The humoral immune response of the *Camelidae* is unique as these animals posses the heavy-chain of antibodies that lack the L-chain, and it was noticed that their H-chain is devoid of the typical first constant domain (CH1) and contains a dedicated variable domain VHH. The VHH exon is assembled from separate V–D–J gene segments. The recombined VHH region is subjected to somatic hyper mutations; however, the timing and actual mechanism of the class switch from μ to the dedicated γ-isotype remains elusive" (abstract). It is noted that Genst describes that "the homology with the human/mouse situation, it is assumed that the successful recombination of a

VH germline gene with a D and a JH germline minigene leads to the expression of a μ-chain associated with the VpreB and λ5 surrogate chains on the pre-B cell membrane."... Genst further states "The situation is far more problematic whenever one of the VHH germline genes recombines with a D–JH assembled product in the pre-B cell. In this event, it remains obscure how such an expressed μ-chain could associate with the surrogate L-chain partners. According to the current idea, the combined VpreB and λ5 complex replaces the BiP chaperon proteins on the H-chain to overcome their retention in the endoplasmic reticulum. The associated VHH domain will supposedly resist VpreB pairing, whereas the CH1 of μ requires the removal of the BiP and concomitant λ5 association for the B cell-membrane display of the H-chain. Hence, it is difficult to envisage the expression of a μ-chain carrying a VHH domain on B cells, since the BiP interacting with the CH1 domain will inhibit transport of the μ-chain to the membrane of the B-cell. Therefore, it might be that cells with a properly recombined VHH-D-J gene associated with a μ chain will fail to start V–JL recombination, but will proceed to a class switch to one of the dedicated HCAb γ genes, possibly by an antigen-independent mechanism-although this remains speculative at the current stage of knowledge (pp 194, col. 1, para 2 bridging to col. 2, para 1). The teaching of Genst clearly suggest that mechanism of pre B cell maturation for the production of VHH single heavy chain was not known rather speculative at the time of filing of this application. It is also not apparent from the specification whether a method as recited in claims would result in fully functional scIgG molecule. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance or any example as to how an artisan of skill would have practiced the claimed method in any mammal by a VH heavy chain locus capable of generating other isoforms of antibodies. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of the B cell maturation of VHH camelid antibody was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a third issue, instant claims 1-4, 7-8, 10-11 and 33-36 are directed to a method for producing a single chain antibody in a nonhuman mammal by expressing a heterologous VHH single chain locus specifically in B cells in response to antigen challenge. The specification contemplates eukaryotic promoters such as alpha-actin, beta-actin, tubulin promoters or, a tissue-specific manner such as promoters of immun globulin genes. In addition, specification also discloses Moloney murine leukaemia virus long terminal repeat (MMLV LTR) promoter, the Rous sarcoma virus (RSV) LTR promoter or the human cytomegalovirus (CMV) IE promoter promoters that may also be used (see para. 101 of the published specification). The specification further contemplates using any of these promoters that are modified by the addition of further regulatory sequences such as tissue-specific enhancers capable of regulating expression in antibody-producing (see para. 102). The art teaches variable effects of different promoters depending upon site of expression. Maruyama et al (US Patent application 20050070014) disclose that the choice of the promoter is instrumental for transgene expression and that the promoter such as CAG is essential, while CMV was not suitable for kidney-targeted gene transfer (see para. 93 of the published application). The breadth of instant claims is very broad and embraces any element that expresses VHH heavy chain locus specifically in B cells. At the time of invention, art of record recognized only mouse as a routinely manipulated animal and recognized the unpredictability of making transgenic animals other than mice using any promoter or construct. For example, Keefer (Animal Reproduction Science 82-83: 5-12, 2004) recognizes the inefficiency of pronuclear microinjection transgenic techniques and the unpredictability of transgene expression when applied to generating transgenic cows, goats and sheep, for example (see page 6, para. 1, line 1 to page 7, line 4). This observation is specifically supported by Hammer et al. (Journal of animal Science, 986, 63, 269-278) who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert et al (Mol Endocrinol. 1988; 2(3): 277-83) report a transgenic pig that did not develop an expected

phenotype of growth during the rapid growth phase, when transfected with a Moloney murine leukemia virus rat somatotropin fusion gene (p. 277, summarized in abstract). The observation is further supported by Mullins et al (Journal of Clinical Investigation, 1996, 97, 1557-1560), who report on transgenesis in the rat and larger mammals. Mullins et al. state "a given construct may react very differently from one species to another" (see Summary section). Given species differences in the expression of various transgenes, one of skill in the art would have been required to undergo undue experimentation to determine which promoters and specific elements of transgene constructs would produce the desired phenotype showing expression of VHH single heavy chain locus in all different nonhuman mammals as broadly recited. In the instant case, the specific elements contemplated by the specification in the construction of vector for use in generating the transgenic nonhuman mammal were not discovered by Applicant, rather they were derived from the prior art based on reports of their function in mice. Absent of evidence to the contrary, it is not clear that these elements would be functional in other animal species in the same manner as they have been demonstrated in the transgenic mouse. Thus, the art of record at the time of the invention does not provide enabling support for the claimed invention of making and using transgenic nonhuman mammal. In addition, claimed phenotype showing expression of VHH heavy chain locus specifically in B cell is unpredictable in any nonhuman mammal. An artisan would have to perform undue experimentation to empirically test different elements of the construct to specifically express the VHH heavy chain in B cells of different species as broadly recited in the instant claims.

As a final issue, the claims 1-4, 7-8, 10-11 and 33-36 embrace a method for producing VHH single chain antibody by expressing a heterologous VHH heavy chain locus in that mammal. The specification asserts loci and vectors may be introduced into an animal to produce a transgenic animal. It is noted that method of inserting the loci into the genome of a recipient animal will be achieved by microinjection or by introducing DNA into embryonic stem cells (ES) cells which can be inserted into a host embryo to derive transgenic mice (pp 27, lines 21-31 bridging to pp 28 see entire section). The state of prior art summarized by Cameron (Molecular Biotechnology 7:

253-265) describes that the art of making a transgenic nonhuman animal is not predictable because of several factors. It is noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or complete absence of expression, as well as less common problems, such as leaky expression in non targeted tissues. A feature common to any transgenic experiments is unpredictable transgenic lines produced with same construct frequently displaying different levels of expression. Further, expression levels do not correlate with number of transgene copies integrated. Such copy number independent expression pattern emphasizes the influence of surrounding chromotin on the transgene" (pp 256; section 4 on transgene regulation and expression). Furthermore Kolbe et al also describe "the expression of foreign gene in transgenic animals is generally unpredictable as transgenes integrated at random after pro nuclear injection into fertilized oocytes" because of inhibition of neighboring chromatin (Kolb et al, 1999, Gene 227, 21-31, abstract). In addition, the method of transgenic nonhuman animal, such as those employed in the instant specification requires embryonic stem cell. Houdebine et al (Journal of Biotechnology, 1994, Vol., 34, pp 269-287) describe that although ES cells can be used to generate transgenic animals, but this approach remains restricted to mice, ES cells from other species are not presently available (pp 279). In addition, Mullin et al also point that non-mouse ES cell capable of providing germ line chimeras were not available (Mullins et al., Journal of Clinical Investigation, 1996, pp 1557, 1st paragraph). Thus, the state of the art is such that ES cell technology is generally limited to the mouse system and that only putative ES cells exist for other species (Moreadith et al., J. Mol. Med., 1997 p214, abstract, Hochepied et al (Stem Cells, 2004, 22, 441-447; abstract). Thus, in view of the prior art and lack of guidance provided in the specification, only mouse ES cells would be enabled to produce any transgenic mice.

The cited arts clearly indicate an unpredictable status of the class switching art pertaining to recombined VHH region assembled from separate V-D-J gene segments. In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples

demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of producing VHH single chain antibody in a mammal by expressing heterologous recombined VHH region assembled from separate V-D-J gene segments as recited in claims. An artisan of skill would have required undue experimentation to develop/design a suitable vector and practice the method as claimed because the art of class switching and vector design was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant's arguments filed November 14, 2006 have been fully considered but they are not fully persuasive. Applicants in their argument on pages 14-15, assert that working examples are not required. Applicants further assert that claims, as amended, recite that the expression is B-cell specific. Applicants argue that cell specific transgene expression in transgenic mammals was an established technology as of the priority date of the present invention-LCR elements were known to provide integration site independent, tissue specific expression of the incorporated transgene in mammalian genomes. Applicants further argue that this enables expression of the VHH or camelised VH locus in B-cells. Applicants also cite in support of enablement a recently published paper showing Applicants have generated both IgG and IgM heavy chain only antibodies in mice following the disclosure of the specification as filed. Specifically, the cited paper discloses the expression of loci containing IgM and IgG, and IgG only, human constant regions, lacking CH1, with two camelid VHH regions, and human D and J regions in mice. Bac clone 11771 and pFastBac were used successfully and the loci further contained FRT and LoxP sites, and immunoglobulin LCR. The vectors are injected into fertilized mouse eggs of animals that do not produce surface IgM and have a block in B cell development at the pre-B cell stage.

In response, Examiner agree that working examples are not required but it is emphasized that the breadth of amended claims embrace expressing a heterologous

VHH heavy chain locus specifically in B cells of any nonhuman mammal in response to antigen challenge using any mean. The art teaches variable effects of different promoters depending upon site of expression. This is supported by numerous studies showing that given construct may react very differently from one species to another. The specification only provides general guidance for using tissue specific promoters (supra). In absence of any specific guidance and given species-specific differences in the expression of various transgenes, an artisan would have to perform undue experimentation and make new inventions in order to practice the method as claimed. In the instant case, the specific elements contemplated by the specification in the construction of vector for use in generating the transgenic nonhuman mammal were not discovered by Applicant, rather they were derived from the prior art based on reports of their function in mice. Absent of evidence to the contrary, it is not clear that these elements would be functional in other animal species in the same manner as they have been demonstrated in the transgenic mouse. In addition, this is further supported by Sigmund et al describing that "the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund et al Arteroscler Throm Vasc Biol 20:1426, col 1, par 1, lines 1-7, 2000). While the intent is not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic nonhuman mammal (emphasis added) with any specific phenotype, it would have required undue experimentation to establish the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype.

It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d*

at 2013 (Fed. Cir. 1994), citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991)*. An artisan would have to perform undue experimentation to determine the appropriate tissue specific promoter or locus control regions (LCR) that would specifically express VHH heavy chain locus specifically in B cell of any nonhuman mammal (emphasis added).

In response to applicant's argument that applicants disclose the expression of VHH heavy chain loci in post filing art. It is noted that the method upon which applicant relies uses specific vector, LCR elements that is injected into a fertilized mouse egg of an animal that do not produce surface IgM and have a block in B cell development at the pre-B cell stage. It is emphasized that instant claims read on expressing vectors of the present invention into any animal to produce a transgenic nonhuman mammal. The specification teaches, "animal may be ... mammal, preferably, a non-human mammal such as a rodent and even more preferably a rat or mouse. In this regard, it is also preferred that the recipient animal is incapable of producing antibodies that include light chains or at the very least has a reduced capacity to produce such antibodies" (see para 128 of the published application). The guidance provided by the applicants gives invitation to others to try different existing transgenic knockout nonhuman animals incapable of producing antibodies that include light chains to express VHH heavy chain loci as contemplated in the instant application. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Examiner has cited references to demonstrate nonhuman transgenic animal with a given phenotype are sensitive to numerous factor at the time of filing of this application (supra). Examiner has also supported the reference of Cameron (Molecular Biotechnology 7: 253-265, 1997) with Houdebine et al (Transgenic Research, 2000, 9, 305-320) showing there were known problem with transgenesis in which the utilized promoter is not expected to work (see page 310, column 2). Houdebine et al while reviewing the work describe that numerous experiments have shown that the level and specificity of the expression of a gene construct cannot be easily predicted. DNA addition by microinjection generates lines of animal expressing the foreign gene at quite different levels (see page 309, col.

2, last paragraph). Thus, it is apparent that in order to practice the method and construct as broadly recited an artisan would have to express transgene with different promoter or elements in different nonhuman animal to achieve specific phenotype of specific expression in B cells. While the intent is not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled in view of breadth of claims and disclosure provided by the applicants. Given such differences in the expression of a transgene, particularly when taken with the lack of specificity in the specification to make any transgenic nonhuman animal, it would have required undue experimentation to attain the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype of expression of VHH heavy chain loci specifically in B cells. Thus, it is clear that at the time of filing of this application transgenesis in any nonhuman animal was not predictable and subject to variable expression depending on the elements of the construct.

New- Claim Rejections- Necessitated by Amendments - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7-8, 10-11 and 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is noted that instant claims contemplate expressing VHH heavy chain locus in B-cell of any nonhuman mammal, but the claim does not set forth any steps involved in method/process, it is unclear what method /process applicant is intending to encompass. The claim merely recites a method without any active, positive step delineating how claimed method step will actually be practiced. The omitted steps are: how expression of heterologous VHH heavy chain locus specifically in B cells of the nonhuman mammal would be achieved? Appropriate correction is required.

New-Claim Rejections-Necessitated by claim amendments - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Ledbetter et al (WO 99/42077, dated 08/26/1999, IDS).

Ledbetter et al teach expressing VHH gene sequence in animals by transgenic technology to make founder animals that expresses llama VHH (pp 32, lines 4-5). Further, Ledbetter contemplates using retroviral or pronuclear microinjection of gene targeting in ES cells to produce transgenic clones containing VHH transgene (pp 32, para. 3, lines 15-23). In addition, Ledbetter also describes a multi specific molecule that may be produced by recombinant expression of polynucleotide that encodes these polypeptides that are single chain polypeptide. Ledbetter et al also disclose that camels secrets antibodies devoid of light chain. It is noted that Ledbetter teaches that the variable region of such heavy chain VHH are fused directly to a hinge region, which is linked to the CH2 and CH3 domains (pp 18, lines 2-4). It is emphasized that a vector comprising a VHH heavy chain locus transfecting a host cells inherently would contain a functional VHH region and a constant region leading to the formation of a single chain antibody. It is also noted that Ledbetter et al also disclosed method to produce VHH monoclonal and polyclonal antibodies in the transgenic animal in response to antigen challenge (see page 33, para. 2-3 and page 34, para. 2). Since Ledbetter contemplated producing monoclonal antibody by immunizing the transgenic mice, expression of heterologous VHH heavy chain locus in B cells in response to antigen challenge is inherent, therefor instant method steps meets the limitation of claims 1-3.

Accordingly, Ledbetter anticipates claims 1-2.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1-4, 7-16 rejected under 35 U.S.C. 103(a) as being unpatentable over Lonberg et al (US Patent no 5874299, dated 2/23/1999) and Riechmann et al (J Immunol Methods. 1999; 231(1-2): 25-38) is withdrawn in view of amendment to claims 1 and 3 now requiring expression of VHH heavy chain in the nonhuman mammal specifically in B cell in response to antigen challenge.

Claims 1-16 rejected under 35 U.S.C. 103(a) as being unpatentable over Lonberg et al (US Patent no 5874299, dated 2/23/1999); Riechmann et al (J Immunol Methods. 1999; 231(1-2): 25-38 and further in view of Green et al (US Patent Application no 20030093820, dated 11/30/2001, effective filing date 6/8/2000) is withdrawn in view of later filing date of Green et al as compared to priority date of instant application.

New- Necessitated by amendments-Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 7-8, 10-11 and 33-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 7-8, 10-11 and 33-36 of copending Application No. 10/692,918. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of producing a single heavy chain antibody in a nonhuman mammal by expressing the a heterologous VHH heavy chain locus specifically in B cells in response to antigen challenge. Subsequent claims limit the VHH to be of camelid or human origin. It is noted that instant claims and dependent claims contemplated single heavy chain antibody by expressing VHH or camelised VH heavy chain also embraced similar imitation. Certain of the instant broader claims differ only with respect to a broader scope of constant heavy chain, which encompass those specifically claimed in '918.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims allowed

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Lonberg et al (US Patent No. 5569825, dated 10/29/1996, art of record).

Riechmann et al (J Immunol Methods. 1999; 231(1-2): 25-38, art of record).

Grosveld et al (Cell, 51, 1987, 975-985, art of record).

Bruggemann et al (Immunology Today, 1996, 17, 391-397, art of record).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
Au 1632

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER